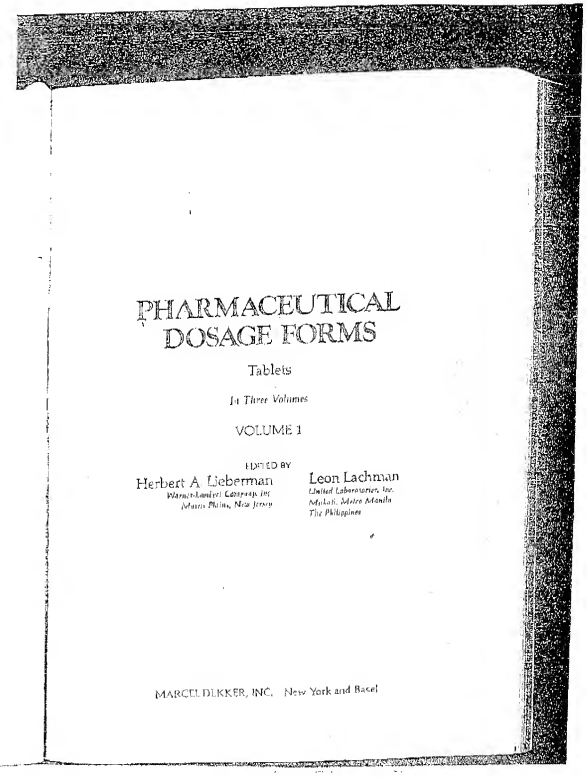

PHARMACEUTICAL DOSAGE FORMS

Tablets

In Three Volumes

VOLUME 1

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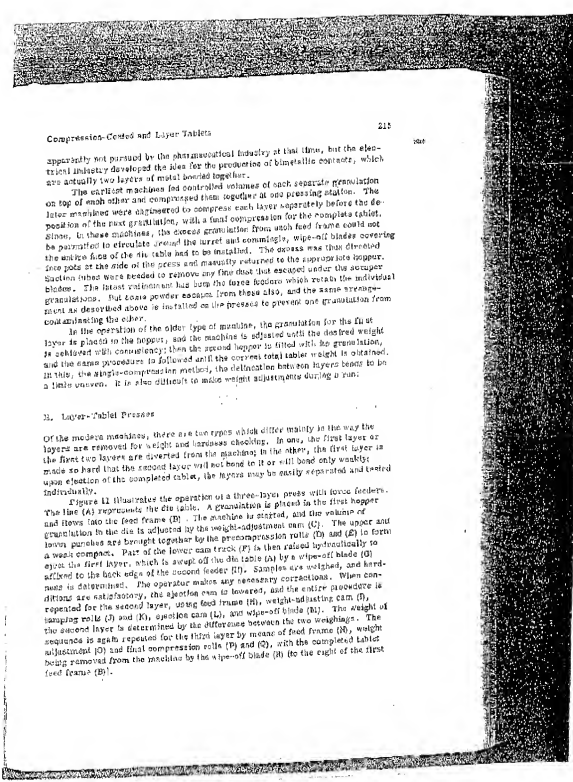

apparently not pursued by the pharmaceutical industry at that time, but the electrical industry developed the idea for the production of bimetallic contacts, which are actually two layers of metal bonded together.

The earliest machines fed controlled volumes of each separate granulation on top of each other and compressed them together at one pressing station. The later machines were engineered to compress each layer separately before the deposition of the next granulation, with a final compression for the complete tablet. Since, in these machines, the excess granulation from each feed frame could not be permitted to circulate around the turret and commingle, wipe-off blades covering the entire face of the die table had to be installed. The excess was thus directed into pots at the side of the press and manually returned to the appropriate hopper. Suction tubes were needed to remove any fine dust that escaped under the scraper blades. The latest refinement has been the force feeders which retain the individual granulations. Put loose powder escapes from these also, and the same arrangement as described above is installed on the presses to prevent one granulation from contaminating the other.

In the operation of the older type of machine, the granulation for the first layer is placed in the hopper, and the machine is adjusted until the desired weight is obtained with consistency; then the second hopper is filled with the granulation, and the same procedure is followed until the correct total tablet weight is obtained. In this, the single-compression method, the delicate balance between layers tends to be a little uneven. It is also difficult to make weight adjustments during a run.

B. Layer-Tablet Presses

Of the modern machines, there are two types which differ mainly in the way the layers are removed for weight and hardness checking. In one, the first layer or the first two layers are diverted from the machine; in the other, the first layer is made so hard that the second layer will not bond to it or will bond only weakly upon ejection of the completed tablet, the layers may be easily separated and tested individually.

Figure 11 illustrates the operation of a three-layer press with force feeders. The line (A) represents the die table. A granulation is placed in the first hopper and flows into the feed frame (B). The machine is started, and the volume of granulation in the die is adjusted by the weight-adjustment cam (C). The upper and lower punches are brought together by the precompression rolls (D) and (E) to form a weak compact. Part of the lower cam track (F) is then raised hydraulically to eject the first layer, which is swept off the die table (A) by a wipe-off blade (G) affixed to the back edge of the second feeder (H). Samples are weighed, and hardness is determined. The operator makes any necessary corrections. When conditions are satisfactory, the ejection cam is lowered, and the entire procedure is repeated for the second layer, using feed frame (H), weight-adjusting cam (I), sampling rolls (J) and (K), ejection cam (L), and wipe-off blade (M). The weight of the second layer is determined by the difference between the two weighings. The sequence is again repeated for the third layer by means of feed frame (N), weight adjustment (O) and final compression rolls (P) and (Q), with the completed tablet being removed from the machine by the wipe-off blade (R) to the right of the first feed frame (B).

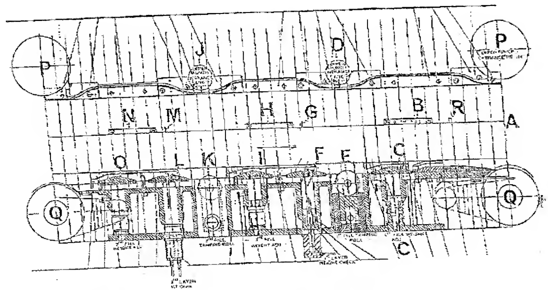

Figure 11. Schematic of a layer press. Refer to text. (Thomas Engineering.)

Compression Coated and Layer Tablets

When a layer is ejected, the upper tamping roll is lowered slightly to exert the more pressure upon the layer. This action will prevent damage to the layer as it strikes the take-off blade and is directed into the collection box. Once the lower punches have cleared the next filling station, they are quickly pulled down by a lowering cam so that they are not struck by the upper punches. The latter are already descending into the dies to make the next tamping or compression stroke.

The leading and trailing edges of each feed frame are equipped with wipe-off blades which divert any powders that escape from the feeders into collection boxes. The blade on the trailing edge of the first feed frame guides the completed tablets down the chute (G) to the collection box. Vacuum tubes in each filling unit suck away any powder or granulation that remains in the lower punch holes during weight checks. Although the punches are raised flush with the die table at this time and do not drop as they pass under the feed frames, they do trap a small amount of material in the depressions in their tips.

If an adjustment to the weight or thickness of the first or second layer is necessary, then the weight of each succeeding layer will probably need correction, since weight is related to the fill volume.

The second type of machine is similar to the one described above, except for the manner in which weight checking is handled. Instead of a cam arrangement for ejecting the layers, the pressure on the first layer is increased, and the layer is made so hard that the next layer will not bond to it. This weld layers are easily separated *few* weighing. This effort is achieved by activating a pneumatic cylinder which raises the lower tamping roll. There is an adjustment to control the distance that the compression roll may rise. Embossed or engraved upper punches provide a key between layers and tend to hold them together. Gentle shaking may be required to separate the layers in this case. Table 3 provides specifications for several typical layer presses currently available.

V. Formulations (Layer)

As with compression-coated tablets, the granulation for layer tablets should be readily compressible for good bonding between layers. Desirable fines should be kept to a minimum; the less dust, the cleaner the scrape-off at each feed frame. It may be necessary to separate out that fraction of a granulation which is finer than 70 or 80 mesh. Such material is not discarded but added to the next lot and regranulated. Lubricants, however, must be finely divided, their efficiency depending on the degree of fineness. Since these lubricant fines cannot be avoided, the quantities used should be kept minimal. The metallic stearates present an additional difficulty in that they interfere with the bonding of the layers. Stearic acid and the hydrogenated fats are better lubricants from this point of view. Nevertheless, granules should be small, less than half the thickness of the layers; otherwise, the lines of demarcation between layers will be uneven.

Equal weights of granulation will not necessarily lead to equal thickness of the layers. That will depend on the compression ratios of the formulations. It may be compensated for by adjusting the weights required for each layer. (It is not necessary, however, that each layer have the same thickness.) The shape of the punches also plays a role: punches with beveled edges or concave faces will make the top and bottom layers of a three-layer tablet appear thinner than the middle one. Plain-faced tooling will produce equal thickness of the layers, but

Table 3

Specifications for Some Layer Presses

Specification	Manufacturer and model designation					
	Manesty 39	Manesty 47	Manesty 55	Manesty 61	Kilian RU-3S	Stokes 506-2
Number of dies	39	47	55	61	20	45
Maximum pressure (tons in.$^{-2}$)	6 1/2	6 1/2	6 1/2	4	8 1/2	4
Maximum tablet diameter	5/8 in.	7/16 in.	7/16 in.	7/16 in.	20 mm	5/8 in.
Depth of fill	11/16 in.	11/16 in.	11/16 in.	11/16 in.	15 mm	11/16 in.
Maximum layer thickness (prior to pressing)						
First layer	1/4 in.	1/4 in.	7/16 in.	7/16 in.	7 mm	1/16 in.
Second layer	1/4 in.	1/4 in.	1/4 in.	1/4 in.	7 mm	1/4 in.
Third layer	1/4 in.	1/4 in.	--	--	7 mm	1/4 in
Maximum output (tablets per minute)	1250	1500	5500	5550	417	2100

Figure 12. Cross sections of layer tablets.

unfortunately the edges of the tablets will tend to chip readily. Figure 12 shows cross sections of layer tablets and illustrates how the shape of the upper punch determines the shape of the layers. If the upper punch faces have monograms or other markings, the bonding between layers will be strengthened because the de-vices will act as keys between the layers. Additionally, precompression lengthens dwell time and aids in bonding. The formulas previously given for compression-coated tablets will serve as a guide for the development of formulations for layer tablets, with the exception of two of those for direct compression [Examples 1 and 2], which are composed entirely of fine substances.

An illustrative formula is one for an analgesic-antipyretic decongestant containing aspirin and phenylpropanolamine. A thin layer of placebo is placed between them to negate the chemical incompatibility of the active ingredients.

Example 1c: First Layer of Analgesic-Antipyretic Decongestant

Ingredient	Quantity per tablet
Phenylpropanolamine HCl NF	12.50 mg
Lactose USP	76.50 mg
Sucrose USP	4.00 mg
Talc USP	3.00 mg
Tragacanth USP	2.00 mg
Polyethylene glycol 6000 USP	4.00 mg
Purified water USP	q.s.
Anhydrous alcohol	q.s.

Screen where necessary to break down agglomerates or lumps (20 mesh screen is satisfactory) and blend the phenylpropanolamine, lactose, sucrose, talc, and tragacanth. Combine the purified water and alcohol and dissolve the polyethylene glycol in the mixture, using heat (60 to 80°C). Add this solution to the mixed powders. Continue mixing until the mass is evenly moistened and granular. Use additional water-alcohol, if necessary.

Dry in an oven with circulating, dehumidified air at 40°C. Pass the dried granules through a 20 mesh screen on a Fitzmill or Tornado mill running at medium speed with knives forward.

Example 16: Second Layer of Analgesic-Antipyretic Decongestant

Ingredient	Quantity per tablet
Lactose USP	48.000 mg
Confectioners sugar USP	24.000 mg
Starch USP	7.070 mg
FD&C color	0.005 mg
Purified water USP	q.s.
Stearic acid USP	0.925 mg

Push the lactose and confectioners sugar through a 20 mesh screen and blend them with the starch in a suitable mixer. Dissolve the color in the water and add to the mixed powders. Continue mixing until the color is uniformly dispersed and the mass is granular. Dry in an oven at 40 to 45°C to a moisture content of 2% or less. Pass the dried material through a 20 mesh screen on a Tornado comminuting machine. Return the granules to the mixer and add the stearic acid. Mix for 10 min.

Example 17: Third Layer of Analgesic-Antipyretic Decongestant

Ingredient	Quantity per tablet
Aspirin-Starch (20 mesh granules, 20% starch)	80.0 mg
Talc USP	20.0 mg

Blend in a suitable mixer until homogeneous (10 to 15 min).

Compress the three layers together using 3/8-in. diameter, flat-faced, beveled-edge punches. The weight of each layer is:

First layer, 100 mg
Second layer, 80 mg
Third layer, 100 mg

The top layer is the last layer to be pressed. Since it is the aspirin portion, it will be most resistant to extrusion from the dies.

Layer presses find employment in the manufacture of chewable antacid tablets. A possible formula for such a product follows. The mannitol provides pleasant mouth-feel and sweetness, and the saccharin enhances the latter. Peppermint flavoring has a long and honorable association with antacid preparations. The

sucrose acts as the binder, although, of course, it also contributes to the taste of the tables.

Example 18: First Layer of Chewable Antacid Tablet

Ingredient	Quantity
Magnesium oxide, heavy	200.0 mg
Mannitol NF	400.0 mg
Sucrose USP	80.0 mg
Saccharin sodium	1.0 mg
Purified water USP	q.s.
Magnesium stearate USP	7.0 mg
Peppermint oil	4.0 mg

Blend the magnesium oxide, mannitol, and saccharin in a double-arm mixer. Dissolve the sucrose in double its weight of water and add to the blended powders. Continue mixing until a moist, granular mass is formed, using additional purified water if necessary. Pass the moist mass through a #8 perforated plate on a Fitzmill operating at low speed with hammers forward. Spread the material on trays and dry at 60°C. Pass the dried granular through a 16-mesh screen on a Fitzmill running at medium speed with knives forward. Return the granules to the mixing machine and add the peppermint oil. When the oil has been thoroughly dispersed, add the magnesium stearate. (If the oil is not added before the lubricant, the tablet will have oil spots on its surface.) Compress the layer at 677 mg using 5/8-in. diameter punches with flat faces and beveled edges.

Example 19: Second Layer of Chewable Antacid Tablet

Ingredient	Quantity
Aluminum hydroxide (dried gel)	900.0 mg
Mannitol USP	400.0 mg
Saccharin sodium	0.6 mg
Starch USP	32.0 mg
Purified water	180.0 mg
Oil of peppermint	3.4 mg
Magnesium stearate USP	7.0 mg
Color	q.s.

Blend the aluminum hydroxide, mannitol, and saccharin. Dissolve the color in the water and add the starch. Heat the mixture on a waterbath until the starch jells and forms a paste. Use the paste to granulate the blended powders. Add more water, if necessary, to form a lumpy mass. Pass this mass through a #8 perforated plate on a Fitzmill running at low speed with hammers forward. Spread the material on trays and dry at 60°C. Pass the dried granules through a 12 mesh screen on a Fitzmill running at medium speed with knives forward. Return the granules to the mixer. Add the flavor first and then the magnesium stearate. Compress at 643 mg onto the first layer.

From the patent literature [14] there is this example of a three-layer tablet.

Example 20: Bottom Layer of Three-Layer Tablet

Ingredient	Quantity
Acetylsalicylic acid	210.0 g
FD&C Yellow No. 5	4.0 g
Cornstarch	30.0 g
Talc	12.0 g
Chloroform	q.s.

Mix thoroughly and pass the mixture through a hammer mill. Add sufficient chloroform to obtain a wet granulation. Reduce the granules to a range of 20 to 40 mesh and dry overnight at a temperature of 120 to 140°F.

Example 21: Middle Layer of Three-Layer Tablet

Ingredient	Quantity
Phenacetin	160.0 g
Caffeine	15.0 g
Phenyltoloxamine dihydrogen citrate	30.0 g
Cornstarch	4.0 g
Powdered sugar	5.0 g
Distilled water	q.s.
Magnesium stearate	3.0 g

Blend the phenacetin, caffeine, and phenyltoloxamine dihydrogen citrate. Prepare a paste by heating the starch and sugar in the water. Add the paste to the powders and form granules. Dry the moist mass overnight at 120 to

140° F. Reduce the mass to granules of about 20 mesh. Blend the granules with the magnesium stearate.

Example 22: Top Layer of Three-Layer Tablet

Ingredient	Quantity
Potassium phenethicillin	125.00 g
FD&C Red No. 3	0.03 g
Chloroform	q.s.
Magnesium stearate	3.00 g

Blend the first two ingredients and pass them through a hammer mill. Add sufficient chloroform to make a hard rubber-like mass. Break up the mass and dry overnight at 130 to 140° F. Reduce the dried material to about 20 mesh granules. Blend the granules with the magnesium stearate.

Using a three-layer press, compress the bottom layer at 254 mg, the middle layer at 197.6 mg, and the top layer at 125.03 mg.

Today, FD&C Yellow No. 5 would not be used with acetylsalicylic acid because of the possibility of allergic reactions.

Although compression-coated and layer tablets are a modest fraction of solid oral dosage forms, they provide two additional alternatives in solving formulation problems. They tend to be more expensive to manufacture than other tablets (except tablet triturates) because of the multiple granulations needed and the slowness of the special presses used.

References

1. Noyes, P. J., British Patent 559996 (1896).
2. Stokes, F. J., U.S. Patent 1,248,571 (1917).
3. DeLong Gum Company. British Patent 430,534 (1930).
4. Kilian, F., British Patent 464,901 (1937).
5. Cooper, J., Pasquale, D., and Windheuser, J., U.S. Patent 2,857,313 (1958).
6. Wolff, J., U.S. Patent 2,757,124 (1956).
7. Blubaugh, F., Zapapas, J., and Sparks, M., J. Amer. Pharm. Assoc. [Sci. Ed.], 47,12;857-870 (1958).
8. Windheuser, J., and Cooper, J., J. Amer. Pharm. Assoc. [Sci. Ed.], 45,8; 542 (1956).
9. Lachman, L., Speiser, P., and Sylwestrowicz, H., J. Pharm. Sci., 52,4; 379-390 (1963).
10. Boswell, C., U.S. Patent 3,048,526 (1962).
11. Bushwalter, F., Granatek, A., and DeMarlo, M., U.S. Patent 3,121,044 (1964).

Suggested Reading

Remington's Practice of Pharmacy, 15th ed., Mack Pub., Easton, Pa., 1975.
Rifenel, W. A., Die Tablette, Editio Cantor KG, Aulendorf i. Wuertt., Germany, 1966.